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THE PRESENT STATUS OF OVARIAN THERAPY *

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In a paper read before the American Association for the Study of Internal Secretions in 1922, I[1] presented an appraisal of ovarian therapy which, from the evidence then available, was of necessity a rather pessimistic one. Since then there has been a remarkable advance in our knowledge of the physiology of the sex cycle. My purpose in the present communication is to review the general problem in the light of our new knowledge, and to consider how much, if anything, this increased knowledge of the physiology of reproduction has added to the rationale and the results of ovarian therapy.

It is along the lines of physiology that the most important advances in gynecology are being made. Contributions are being made so rapidly that no present point of view should be urged too dogmatically or too inflexibly. The subject is still too liquid to justify this, although each year new facts are being crystallized out. Clinical workers must be guided largely by the results of those who are studying the problem in laboratories. The latter are still in disagreement over a great many points. It would be unfortunate if the eager clinician should apply half-proved theories or speculative hypotheses to his own problems. This is just what we have been doing for the past thirty years, and this is why there has been so much discouragement with the whole subject of ovarian therapy.

A mere review of the now huge literature, within the limits of a reasonably short paper, would of necessity be sketchy, inconclusive and probably uninteresting. I have therefore thought that a rather general appraisal, based on a reasonable familiarity with the literature of both clinical and laboratory investigations, and a fairly extensive personal experience with ovarian therapy, might be more worth while. The views here expressed, therefore, represent merely a personal reaction to the whole subject as it presents itself today.

OVARIAN PREPARATIONS AVAILABLE, AND THE METHOD OF EMPLOYMENT

Ovarian Preparations for Oral Administration.—These can be dismissed rather briefly, because they are familiar to every one, and because I can add little new to what was said concerning this subject in my previous review. They are made from the entire ovary, or from the corpora lutea alone, or from the "ovarian residue"; i. e., that portion of the ovary remaining after removal of all corpus luteum tissue. The first two types are used much more extensively than the third. All of them are available in the form of tablets, capsules or powders. The majority of manufacturers, for the sake of securing smoother preparations, include in the process of manufacture some form of "degreasing," which removes fatty principles which, on the basis of laboratory investigations, are considered to be of much importance, as they are in some way bound up with the active principle of the ovary. There is no standardization of these preparations, nor is there likely to be in their present form, because of the fact that laboratory tests show them to be without any demonstrable biologic action. They do not, for example, possess any such estrus-producing effect in spayed laboratory animals as is shown by the follicle hormone.

"Ovarian residue" was suggested by Graves[17] in 1919 on grounds which were anything but convincing, because there was certainly no evidence at that time to indicate that the interstitial elements of the ovary are of any physiologic importance in the human being. Nor is there any such evidence now, although, in the light of the newer work on the follicle hormone, it is true that "ovarian residue" may contain an incidental, though always small and uncertain, amount of follicle tissue. If one wants to administer follicle substance by mouth, however, there are far more potent and more precise ways of doing so than by means of ovarian residue. For example, placental tissue contains a large amount of follicle hormone, and the use of placental extracts would seem to have some scientific basis.

So far as I know, no American manufacturer has yet undertaken to supply a follicle hormone preparation suitable for administration by mouth, although one or two such preparations have been made available in Germany. Follicle substance is difficult enough to obtain in the far smaller amounts necessary for hypodermic administration, for it has been shown by Loewe, Lange and Faure[18] that, while the oral route is effective even in the production of estrus in castrated animals, at least twenty times the hypodermic dose is required.

With regard to the older forms of ovarian preparations mentioned, there is no worth-while evidence to indicate that they are of any particular value in the relief of objective symptoms of hypofunction of the ovary. It is true that scattered reports are to be found of occasional cases in which their employment in such

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* Owing to lack of space, this article has been abbreviated in THE JOURNAL. The complete article will appear in the Transactions of the Section and in the author's reprints.

* Read before the Section on Obstetrics, Gynecology and Abdominal Surgery, at the Seventy-Ninth Annual Session of the American Medical Association, Minneapolis, June 15, 1928.

1. Novak, Emil: An Appraisal of Ovarian Therapy, Endocrinology **6**: 599 (Sept.) 1922.

17. Graves, W. P.: Ovarian Organotherapy, J. A. M. A. **69**: 701 (Sept. 1) 1917.

18. Loewe, S.; Lange, F., and Faure, W.: Die Wirksamkeit des Zyklushormons bei peroraler Zuführung, Deutsche med. Wchnschr. **52**: 310 (Feb. 19) 1926.

conditions as amenorrhea has been followed by menstruation. Such reports, however, are rarely of such a character as to impress one with their scientific significance. Without going into detail, I believe that there are few dispassionate observers who will maintain that the oral administration of these preparations for such indications is of any great value. This question will be discussed more fully in connection with the objective indications for ovarian therapy, as will the employment of such preparations in the subjective symptoms of the menopause, in which there is more room for an honest difference of opinion.

The most important reason for the general inefficacy of these preparations is, first of all, the fact that there is much reason to doubt whether they contain any appreciable amount of the active principle or principles of the ovary. Whether this is due to the fact that the ovarian tissue from which they are prepared contains very little stored-up secretion, or whether the secretion is destroyed by the method of manufacture, cannot be stated. Furthermore, there is much reason to believe that the active principle of the ovary is destroyed by the alimentary juices. Finally, if it is true, as many of us believe, that menstruation is the end-result of a series of orderly changes occurring in the endometrium as a result of the action of more than one ovarian secretion in proper amount and proper sequence, it is difficult to see how a tablet made from an animal ovary at one particular phase of its cycle—and that not always the same—can bring about normal menstruation in the woman to whom it is administered, especially as her sex cycle is so different from that of the animal.

In the manufacture of practically all the older forms of preparations for oral administration, no especial effort is made to select ovaries with reference to the phase of greatest functional activity of the follicle or corpus luteum, nor would this usually be feasible on a commercial basis. Hence, even from a theoretical point of view, there could not be any such thing as uniformity, and many of the ovaries utilized must be devoid of any active principle whatever.

Preparations for Hypodermic Administration.—Even before the discovery of the physiologic potency of the follicle hormone in laboratory animals, the poor results of oral ovarian therapy for most indications had suggested the hypodermic route of medication. But the hypodermic use of aqueous and lipoidal extracts, which soon became increasingly popular, gave little more reason for satisfaction. In addition, this method of administration presented certain obvious objections which made its application very limited, as will be emphasized later in this paper.

With the new knowledge of the potency of follicle hormone, a new hope has been kindled, and manufacturers are striving earnestly to produce preparations which will yield clinical results. Some of these preparations, formerly available only to the experimental investigator, are now at the disposal of the general profession, though still in limited amount and at rather high cost to the patient. Various names have been given to the supposed active principle by different laboratory workers and different manufacturers, such as folliculin, oestrin, oestrogen, feminin, menformon and thelykinin. All of these are for hypodermic use only, in spite of the fact that an increasing number of observations indicate that even by mouth the principle exerts an estrus-producing effect on spayed animals. Since the dosage required by mouth, however, is at least twenty, and, according to some, many more times as great as that necessary for hypodermic use, this consideration alone, in the present scarcity of the material, makes the latter route the preferable one.

It soon became apparent that the follicle fluid of animals would furnish a very insufficient supply of the active principle for clinical purposes, so that most of that now made is derived from the placenta, which is known to contain a considerable amount. The method of preparation is tedious, and no manufacturer is as yet producing the active substance in any large amount. New sources of supply are being sought. Fraenkel [19] has suggested that the urine of pregnant women, containing as it does an unusually large amount of the substance, might be utilized as a source of supply. One manufacturing house in this country has recently been able to prepare considerable amounts from the amniotic fluid of cattle.

The discussion of whether to use lipoidal or aqueous extracts illustrates the frequency with which our point of view concerning ovarian therapy must be changed. The importance of the lipoidal elements was formerly urged by practically all investigators, for the lipoids were considered to be in some way bound up with the active principles of the ovary. Recently, however, a number of competent investigators have shown that by proper methods of preparation active aqueous extracts may also be obtained. Practically all workers are still agreed that the lipoidal solutions, however, are to be preferred. They do not deteriorate so readily, and their slower absorbability makes their effect less evanescent.

Much less attention has been paid to the corpus luteum extracts, because of the emphasis that has been placed on the follicle substance as the all-important female sex hormone. This is unfortunate, because, as I have already emphasized, there is much evidence to indicate that the corpus luteum plays a part in the human cycle no less important than that of the follicle. More and more evidence is accumulating to support this view, and already a number of investigators have been able to prepare active corpus luteum extracts which produce effects quite different from, and in some respects antagonistic to, the follicle hormone.

The pioneer work of Loeb [7] had indicated that the corpus luteum secretion is capable of inhibiting ovulation. Papanicolaou,[12] in 1927, reported that, by injecting a corpus luteum extract in guinea-pigs, he could bring about a similar retardation of ovulation, and he emphasizes the fact that the extract is in many respects antagonistic in its effects to that of the follicle fluid. He has not yet, so far as I know, given details as to the preparation of this extract. Margaret Smith [13] likewise produced evidence, not dependent on the use of a corpus luteum extract, to indicate that there must be in the ovary another hormone besides that of the follicle. This hormone, which she feels must be that of the corpus luteum, is antagonistic to that of the follicle in many of its effects, the two constituting a balancing mechanism.

Hisaw,[20] in a recent preliminary communication, has attacked the problem from a new point of view. He found that the pelvic ligaments of the guinea-pig are relaxed by injections of corpus luteum extract, but only when the animal is under the influence or recovering from the influence, of the follicle hormone. He [21]

19. Fraenkel, L.: Ueber das weibliche Sexualhormone, Deutsche med. Wchnschr. **53**: 2107 (Dec. 9) 1927.
20. Hisaw: Tr. Am. Asso. Adv. Sc., 1927, to be published.
21. Hisaw: Personal communication to the author.

concludes that "in order to get certain biologic results the hormones of the follicle and the corpus luteum have to be given in proper sequence."

Another important contribution has been made recently by Weichert,[22] who, working with Hisaw's corpus luteum extract, produced a definite inhibition of ovulation. Furthermore, by injecting the hormone into rats for two days following estrus, then stimulating the uterine mucosa, and continuing the injections for four more days, he produced definite placentomas. Loeb had shown that these could occur only during the active phase of the corpus luteum. Weichert further states that "ovariectomized rats were treated with corpus luteum hormone in the same manner and no placentomata were formed. If, however, such rats were first brought into oestrum artificially by injections of the follicle hormone and then treated as above, placentomata were formed. Apparently the follicular hormone is necessary to put the uterus in a proper physiological condition before it will respond to the corpus luteum hormone."

This work, if confirmed by others, will bear out completely the view I have been urging for some years, that both follicle and corpus luteum hormones are of importance, and that the latter can exert its effect only when the field has been prepared, so to speak, by the follicle hormone.

The Changed Attitude of Some Manufacturers.—It may not be out of place to say a word as to the part played by the better manufacturing houses in the development of this problem. It has been the custom in years gone by for authors of "conservative" papers on organotherapeutic subjects to include more or less scathing denunciations of the evil rôle played by manufacturing houses, through their commercial exploitation of preparations based on unproved and perhaps absurd hypotheses. There are still, as we all know, many manufacturers who heartily deserve such censure. On the other hand, it is only fair to say that there are now a few houses which are making a sincere effort to cooperate with investigators in working out such problems as the one we have been discussing. While the primary motive of such concerns is, of course, a commercial one, they have apparently come to realize that in this day and generation, it would be poor business to exploit preparations which will soon be shown to be worthless. Much time and money is therefore often spent in laboratory investigations of a high standard of excellence, and much willingness is shown by manufacturers to cooperate with other laboratory workers and clinicians in an effort to get at the truth before marketing their wares.

INDICATIONS AND RESULTS

As complete removal of both ovaries invariably brings about cessation of the sex cycle, there can be little criticism of the general theory of ovarian therapy in conditions due to absence or deficiency of ovarian function. The question, however, which at once suggests itself is this: Has our knowledge of the physiology of the cycle and of the biochemistry of the ovary advanced sufficiently to enable us actually to place in the patient's circulation, in appropriate amount, the substance or substances that are secreted by the normally functioning ovary? This question has already been discussed, superficially at least, in the foregoing pages of this paper. It must be clear that, in spite of the great strides of the past few years, there is still much to learn on this subject. I do not, of course, mean to indicate that all efforts at therapy in the human subject should be withheld until our knowledge is more complete. This, indeed, would be a mistake, for, after all, the problem of the human sex cycle can in some of its aspects be studied best, and perhaps only, in the human subject, for the animal cycle differs from the human cycle in many respects. No harm is done the patient by the use of any of the extracts that have been employed.

The important consideration, it seems to me, is that such tentative efforts at a specific therapy should be carried on in the same scientific spirit which we exact from laboratory workers. It would perhaps be better, utopian as the suggestion may be, if the study of the applicability of the newer knowledge of ovarian physiology to the human being were for the time being left to the larger teaching clinics, where ample facilities exist for such a scientific study. For the present the whole problem is in an experimental stage, and premature application of our as yet unripe knowledge will carry in its trail the usual clutter of faulty clinical observations and poorly digested conclusions, so that the issue will be beclouded for years to come.

Among the clinical manifestations which may reasonably be ascribed to hypofunction of the ovary are the following:

1. Amenorrhea (absence of menstruation), hypomenorrhea (scanty menstruation), and oligomenorrhea (abnormally infrequent menstruation), delayed puberty, and premature menopause.

2. The vasomotor symptoms of the menopause (either natural or artificial).

3. Some cases of sterility (probably only a small proportion).

4. Possibly some cases of so-called primary dysmenorrhea, genital hypoplasia, obesity, repeated abortion, and menstrual headaches.

Amenorrhea, Scanty Menstruation and Allied Conditions.—This is not the place to discuss the varied etiology of amenorrhea in general, but it may not be amiss to emphasize the necessity of a careful discrimination of causes as a preliminary to intelligent treatment. For example, amenorrhea in some cases must be interpreted as an effort of nature to conserve the strength of a patient suffering with some serious general disease, such as tuberculosis or anemia. A good illustration of this type of disorder was the "Kriegsamenorrhöe," the widespread prevalence of which among the women of the belligerent nations during the Great War was clearly due to the fact that they were much undernourished. Experimental studies have demonstrated how singularly sensitive the ovary is to dietary deficiencies. In clinical cases of this group the underlying ovarian disturbance and the cause of the amenorrhea is probably an actual failure of ovulation ("anovulation"). It would be both unintelligent and harmful to employ organotherapy in such cases. Similar discrimination must be made as to other causes.

In a considerable group of women otherwise in good health, however, the cause of the menstrual deficiency must be sought in a hypofunction of the ovary, whether this is primary or secondary. The recent studies of Smith and Engle, and of Zondek and Aschheim, already referred to, bear out the clinical impression that a large proportion are of primarily

22. Weichert: Production of Placentomata in Normal and Ovariectomized Guinea-Pigs and Albino Rats, Proc. Soc. Exper. Biol. & Med. **25**: 490, 1928.

hypophyseal origin. But, since the effect of ovarian organotherapy is a purely substitutional one, the amenorrhea would seem amenable to correction, provided one can place a sufficient amount of the ovarian secretion in the patient's circulation.

Attention has been concentrated largely on the follicle hormone as the best substance to use for this purpose. Scattered reports of occasional successful results have been made, but, in the main, the consensus of opinion among those who have used this plan of treatment is that the results have been disappointing. The reason for this, according to many observers, is the fact that the dosage employed has been wofully inadequate. The preparation of the substance is tedious, and high concentrations have not up to this time been possible, because of their rapid deterioration.

My own feeling is that this is not the chief reason for failure, and that the real cause for unsatisfactory results is that in the human being the follicle substance, even in large doses, is not sufficient to bring about a development of the endometrium to its premenstrual phase, and that unless the latter is accomplished, menstruation cannot usually be brought about. The evidence for this belief I have fully discussed elsewhere.

If follicle hormone is employed, it should be administered in large doses, preferably at least 100 rat units, daily for eight or ten days, and then stopped. If menstruation does not occur in four or five days, the injections may again be resumed. It should not be forgotten that menstruation is a "withdrawal" phenomenon, the bleeding being caused by a breaking down of the endometrium which has previously been built up to a sufficiently high point by the hormone injections. In the human female the follicle hormone, which appears to be a growth principle pure and simple, is not capable of building the endometrium up beyond the interval phase, the corpus luteum supplying the final and essential "topping-off," as I have already stated.

For such reasons as this, I believe that neither follicle nor corpus luteum injections alone are as effective as a combination of the two in proper sequence. Eight or ten follicle hormone injections, followed by perhaps six of a corpus luteum extract, should be the proper plan. The difficulty with this plan is the fact that corpus luteum extracts of undoubted efficacy are not yet available, although they have been prepared by a number of laboratory investigators. When such preparations are put into our hands, I believe that ovarian therapy will have made a real advance.

My own clinical observations in this field are similar to those of most others, with usually disappointing results from follicle hormone alone, and slightly better results with the combined plan. The corpus luteum extract which I have employed is of the lipoid-containing type, made at my suggestion through the generous cooperation of the biologic department of Parke, Davis & Co., who have also supplied me with liberal amounts of the follicle substance. The laboratory efficacy of the corpus luteum extract, which I have used, in the inhibition of ovulation has not yet been conclusively demonstrated, although studies are still being made on this point, as also on the question of whether or not, in spayed animals, they will provoke the formation of placentomas when the uterine mucosa is irritated.

Vasomotor Symptoms of the Menopause.—The question of the value of ovarian preparations in the treatment of these subjective symptoms is one of the most interesting and most perplexing aspects of the whole problem. While few clinicians now will maintain that oral ovarian therapy is of much benefit in such objective disorders as amenorrhea, there are a large number who are not only willing but eager to attest its value in the treatment of the characteristic symptoms of the menopause. So competent an observer as Graves,[23] for example, in a recent paper spoke of ovarian therapy as a "near-specific" for this indication. Fraenkel[24] likewise is an advocate of the treatment, reporting not less than 90 per cent of successes (in a later paper, from 70 to 80 per cent). Many other reports of this nature might be quoted, even from those who are cynical of the value of ovarian therapy for other indications.

It is hardly necessary to urge the very great care necessary in drawing conclusions as to the value of any plan of treatment when one is dealing with subjective symptoms. On the other hand, it may properly be argued that the vasomotor flushes are certainly not altogether subjective; that they are usually easily visible to the observer, and that, although undoubtedly influenced somewhat by the patient's psyche, they recur periodically and perhaps frequently in many patients of most phlegmatic temperament. I do not know any objective way of determining the efficacy of any plan of treatment of these symptoms except to determine the effect of the treatment on the frequency and severity of these flushes, after precautions have been taken to eliminate the psychic factor as far as possible.

Two or three years ago I made observations in two small parallel series of cases, in one of which an ovarian preparation (corpus luteum) was given by mouth, while the patients of the other group received a simple tablet of bromides (5 grains, or 0.3 Gm.). In the two sets of patients the same general reassurance and "line of talk" was given. Without going into details, I may say that it was difficult to escape the conclusion that the ovarian preparation was of some value. Patients, for example, who had been having fifteen or twenty flushes during the twenty-four hour period would often report a drop to four or five. It is true that some of the patients who got the bromide were likewise benefited, but not so frequently or markedly as the other group.

Indeed, the results of ovarian therapy in cases of this type are so much less disappointing than in other manifestations of hypofunction that one is led to wonder whether the same hormone can be concerned, or whether the menopausal vasomotor symptoms may not be influenced by far smaller doses than those required for the reestablishment of the menstrual function. This aspect of the problem cannot be solved by laboratory experiments on the lower animals, and, regardless of theoretical considerations, it is pretty certain that ovarian therapy will continue to be used for the relief of vasomotor symptoms.

Furthermore, it is not fair to criticize clinicians too harshly on this point. Is any other method of treatment of these symptoms based on grounds which are any more rational, or does any other give better results? If so, I do not know of it. It goes without saying that any form of treatment should include the usual measures of hygiene, and the building up of the bodily health generally. Even more important is a proper mental reassurance of the patient as to the significance

23. Graves, W. P.: Ovarian Therapy, J. A. M. A. **89**: 1308 (Oct. 15) 1927.

24. Fraenkel (footnote 19); Weibliche Sexualhormone, Zentralbl. f. Gynäk. **52**: 132, 1928.

and temporary nature of these symptoms. After all, the menopause is a physiologic epoch, and only in a comparatively small proportion of cases do its symptoms assume really pathologic proportions. And yet there are many women who approach it with dread, because of distorted ideas as to its effects on body and mind. In no field can the counsel of the intelligent and sympathetic physician be of greater service to the troubled patient than in this.

What may be expected of the newer hypodermic therapy, with follicle hormone or corpus luteum extracts, in this particular field? So far as available reports are concerned, not much, if any more, than is possible with the older oral method. Furthermore, the menopause in many women is dragged out over many months, or even years. Certainly it is too much to expect that women would cooperate very wholeheartedly in a plan of treatment requiring frequent hypodermic injections over a term of years. The compromise which most of us will probably make is to continue oral therapy unless the symptoms become very aggravated, in which case we shall be inclined to interject an occasional course of injections in the hope that they may yield quicker or more decided results. It is possible that subsequent work may change this point of view very materially, but this appraisal is written from the standpoint of such evidence, clinical and laboratory, as is now available.

Sterility.—One hesitates to discuss this subject from the standpoint of organotherapy, because there is so little known as to endocrinopathic causes of sterility. There can be little doubt, *a priori,* that such cases occur, especially when the sterility is combined with amenorrhea. But whether, in any particular case, we are dealing with anovulation or with a deficiency of follicle or of corpus luteum hormone or some other endocrine factor, is obviously beyond our ken at this time. Organotherapy in sterility is still in the empiric stage. The reports of occasional successes can, at the best, mean little more than that a shot in the dark may occasionally find its mark. Nevertheless, in the case of the sterile woman who longs intensely for children, and in whom thorough examination by approved methods has ruled out all other factors—though not until then—I for one would not hesitate to experiment with these at least harmless organotherapeutic measures, preferably hypodermically, in the hope that by a providential strike some unknown block in the endocrine chain might be overcome. But I would do this in full realization of the unscientific nature of the procedure, and in the full expectation of failing in the vast majority of cases. The recent work on the relation of the pituitary to the ovary, to my mind, offers far more hope in the ultimate treatment of endocrinopathic sterility than any development of recent years, but, at this writing, no means of clinically applying this experimental work is as yet apparent.

Other Indications.—In such conditions as those listed in group 4, in which the etiologic rôle of hypogenitalism is far less clearly definable than in those discussed, there is little reason to expect much benefit. If used at all, ovarian therapy, as in cases of sterility, must, in the present state of our knowledge, be employed on empiric or semiempiric grounds, and only because of the fact that in most of these conditions other methods of treatment are equally unscientific and equally apt to be disappointing. In addition to these indications ovarian substances have been used, by either the oral or the hypodermic route, for a host of other conditions such as the vomiting of pregnancy, exophthalmic goiter and epilepsy, in which there is not the slightest reason to expect benefit, and in which not the slightest benefit is ordinarily seen.

HYPERFUNCTION OF THE OVARY

Very little is known about clinical syndromes referable to excessive function of the ovary. Indeed, there is perhaps only one condition in which the scientific evidence for such a hyperfunction is fairly complete. I refer to the so-called functional uterine bleeding, which occurs most frequently at the menopausal age, but which is not rare at or shortly after puberty, although it may be noted at any age during reproductive life. The pelvic organs are characteristically perfectly normal from an anatomic standpoint. There is almost always an associated hyperplasia of the endometrium, which, however, is unquestionably merely the result of the ovarian dysfunction. The evidence for these statements, which I believe to be quite complete, I have presented in previous publications.[25] The characteristic ovarian finding is an absence of corpora lutea and a persistent mature graafian follicle, within which a well preserved ovum may usually be found (Schröder). These histologic conditions, viewed in correlation with the now well known physiologic effects of the follicle hormone, leave little doubt that this type of bleeding is due to an excess of the follicle stimulus and a deficiency of the corpus luteum principle.

The logical treatment would seem to be the injection of corpus luteum extract, and I believe, when an extract of undoubted potency is made available, that it will be possible to control this form of hemorrhage very readily. Even with the extracts now available, it is possible to benefit some of these patients very materially. This is especially true of those in whom the hemorrhage takes the form of menorrhagia rather than metrorrhagia. By daily injections of a lipoid-containing corpus luteum extract for six or eight days before the onset of the abnormal menstruation, the amount of the bleeding is often kept within normal bounds, and patients may often be carried along until the endocrine balance is readjusted; for such a tendency to spontaneous readjustment is present in a considerable proportion of cases. It need scarcely be added that such treatment should never be resorted to until it has been demonstrated, usually by diagnostic curettage, that the hemorrhage is really of this functional nature and not due to some definite anatomic lesion, such as cancer. In the case of younger women, in whom the possibility of future pregnancy is of prime importance, organotherapy is always worth trying before resorting to radiotherapy, which is fraught with many objections in younger patients.

PRACTICAL DISADVANTAGES OF HYPODERMIC MEDICATION

While the superiority of the hypodermic over the oral route for the administration of ovarian preparations appears to have been clearly established, the method carries with it certain objections which make one doubt whether it will achieve more than a limited vogue. Even in the treatment of amenorrhea and allied conditions, a single course of injections entails daily visits to the physician's office for from seven to four-

25. Novak, Emil: Relation of Hyperplasia of Endometrium to So-called Functional Uterine Hemorrhage, J. A. M. A. **75**: 292 (July 31) 1920. Novak, Emil; and Martzloff, K. H.: Hyperplasia of the Endometrium, Am. J. Obst. & Gynec. **8**: 385 (Oct.) 1924.

teen or more days and a certain amount of physical discomfort because of the transient soreness which the injections cause. Furthermore, the evidence indicates that the injections are purely substitutional in their action, and that they do not actually activate the ovarian mechanism itself. For this reason, even if a single course is successful, menstruation is not likely to recur unless the injections are again repeated, and so on month after month.

There are few patients who would have the patience and persistence to keep this up for any great length of time. This is especially true because the condition treated is one that is in no way inimical to perfect health. The occurrence of menstruation is certainly not an essential to physical well being, although, through ignorance of this fact, some women may suffer a good deal of mental perturbation. Aside from a consciousness of being different from others of their sex, they fear the ill effects of amenorrhea, because they believe that the function of menstruation is to throw off bodily impurities. A simple explanation of the real significance of the process does much to relieve the minds of such patients.

Others again, with somewhat better reason, wish to menstruate because of their desire for pregnancy. There is no doubt that in most cases of amenorrhea there is at least a relative, though not an absolute, sterility. This constitutes the motive which, in a large proportion of cases, impels the woman to seek relief from amenorrhea, and fully justifies the physician in attempting its relief.

In the treatment of menopausal symptoms, also, the hypodermic method, as it now exists, seems destined to play only an adjuvant rôle, as emphasized elsewhere in this paper. The menopausal symptoms are not infrequently dragged out, with varying intensity, over a period of years, and it is difficult to quicken the patient's enthusiasm in hypodermic ovarian therapy, especially when one cannot usually promise very brilliant results.

All in all, while there does not appear to be any immediate prospect of developing a preparation satisfactory for oral therapy for all the indications here enumerated, there is no question that this would be a "consummation devoutly to be wished."

SUMMARY

Great as have been the advances of the past few years in our knowledge of the physiology of reproduction, it cannot be said that they have as yet added very notably to the therapy of conditions dependent on disorders of ovarian function. The newer knowledge, however, offers a clear explanation of the failure of the ovarian therapy of past years, and, for the first time, justifies the hope that before long some at least of these functional disorders will be amenable to organotherapeutic measures.

The question as to the singleness or duality of the ovarian secretion is still undecided, although, in my judgment, the evidence indicates that the follicle and corpus luteum hormones are not the same, and that both play important parts in the human sex cycle. This factor, even more than that of inadequate dosage, is probably responsible for the unsatisfactory results achieved from the employment of the follicle hormone itself. For this reason, it is more logical to combine with it the use of corpus luteum extract, imitating the sequence believed to occur in the normal sex cycle.

One of the problems still to be solved, in spite of the encouraging results achieved by individual workers is that of preparing a potent corpus luteum extract. The standards of potency are of course very different from those of the follicle hormone, a fact which some workers appear to overlook.

Both from a clinical and laboratory standpoint, the evidence indicates that the oral administration of ovarian, corpus luteum and ovarian residue extracts has little or no value in the treatment of such objective disorders as amenorrhea. In the treatment of the characteristic vasomotor symptoms of the menopause, there is much evidence, though necessarily only clinical, that oral therapy is of value.

While the hypodermic administration of the newer extracts is, on the basis of undisputed laboratory investigations, without doubt the method to be preferred, it possesses serious practical disadvantages which will almost certainly limit its applicability very materially. These disadvantages, enumerated in my paper, are enhanced for the present by the comparative scarcity of potent extracts and their rather considerable cost. As the ovarian follicle hormone at least possesses a slight effect when administered orally (not more than one-twentieth the hypodermic effect), it is not impossible that some form of satisfactory oral therapy may yet be developed, either by developing new sources of supply or by increasing the potency of the substance by some artificial means. This would be a contribution of real importance.

Recent investigations, which demonstrate the profound effect produced on ovarian function by repeated implantations of anterior pituitary gland tissue, lead to the hope that future work along this line may yield some method of applying this new knowledge therapeutically.

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ABSTRACT OF DISCUSSION

DR. WILLIAM ENGELBACH, St. Louis: I believe that gynecologists and obstetricians take a little one-sided view of both the diagnosis and the absolute end-results of organotherapy on primary and secondary symptomatology, resulting from ovarian insufficiency. The trend of information along this line indicates that there is more than one internal secretion supplied by the ovary. The probabilities are that those coming from the follicle and the corpus luteum have to do with the so-called primary functions of the ovary, ovulation, procreation, and associated signs and symptoms. There probably is an internal secretion from the stroma and the interstitial portion of the ovary similar to that of the testis which has to do with the constitutional or so-called secondary sex complex of the ovary. These correspond to a certain extent to the development of the secondary sex characters and the various psychic vasomotor symptoms following castration and in the menopause. It is difficult for me to make my ideas coincide, however, with the deductions Dr. Novak has drawn to the symptomatology following amenorrhea, which I would attribute to the interstitial portion of the ovary. I cannot agree that these women are comparatively free from symptoms, are happy and have no serious effects from the cessation of the menses. Analyses in a large number of cases showed that they have very serious reactions. Any one who sees a great number of these patients with ovarian insufficiency, either primary or secondary, must realize that they do have very serious constitutional disability. The disability is often extreme; for instance, persistent vomiting, over a long series of years, with very marked nervous and cardiovascular symptomatology so severe as to incapacitate these patients absolutely. It has been my experience in treating a large number of castrates, aged from 15 and 16 years up to late adult life, that positive relief from these symptoms was obtained by giving large doses of ovarian substance hypodermically. We say, and I think conservatively, that in from 25 to 35 per cent of these patients good results have been noted.

DR. EMIL NOVAK, Baltimore: Dr. Engelbach spoke of a possible third secretion from the ovary, derived from the stroma or interstitial cells. This, however, is purely speculative, as I know of no evidence whatever for such a view. In the human ovary there is no histologic element to be demonstrated which is analogous to the interstitial cells of the testis, except during pregnancy, when the so-called thecalutein cells produce what is sometimes called the interstitial gland, considered by many the analogue of the male interstitial cells. I made it plain in my paper that the symptoms of the menopause, while mild and unimportant in many cases, may, in others, be so severe as to necessitate treatment. I certainly do not agree with Dr. Engelbach that amenorrhea frequently produces unpleasant symptoms in itself. I am sure that every gynecologist will agree that in the overwhelming majority of cases the woman complains of few other symptoms than the absence of menstruation. Certainly such symptoms as vomiting and heart disturbances are not characteristic of amenorrhea. If they are present I would be inclined to believe that both these symptoms and the amenorrhea are together due to some underlying condition. We are dealing in this discussion with cases of the usual functional type, rather than with those due to such organic lesions as, for example, pituitary tumors. Many clinicians have used anterior pituitary preparations of one form or another by mouth or by the hypodermic method for many years. Some, like Dr. Engelbach, have reported good results, but I do not think that this is the general experience, nor is it in conformity with laboratory investigations. The work of Smith and Engle, to which I have referred in my paper, indicated that anterior pituitary substance by mouth was worthless. Such studies as this will do much to clarify the relation between the pituitary and the ovary and will serve as a guide to rational organotherapy.